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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,726	11/06/2008	Jack J. Hawiger	21392/1212794-US1	9649

78102 7590 08/16/2010

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
08/16/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/589,726	HAWIGER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-31* is/are pending in the application.

4a) Of the above claim(s) *15,26 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16-19,21-25,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-19 and 21-31* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 03 June 2010 has been entered in full. Claims 1-8, 10, 12-15, 19, 23-26, and 30 are amended. Claim 20 is cancelled.

Claims 15, 26, 29-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04 September 2009.

Claims 1-14, 16-19, 21-25, 27, and 28 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the specification at page 2 of the previous Office Action (06 January 2010) is *withdrawn* in view of the amended specification (03 June 2010).

2. The objections to claims 3, 10, and 19 at pages 2-3 of the previous Office Action (06 January 2010) are *withdrawn* in view of the amended claims (03 June 2010).

3. The rejections of claims 4, 5, 7, 8, and 12 under 35 U.S.C. 112, second paragraph, as set forth at pages 3-4 of the previous Office Action (06 January 2010) are *withdrawn* in view of the amended claims (03 June 2010). Please see section on 35 U.S.C. 112, second paragraph below.

4. The rejection of claim 4 under 35 U.S.C. § 102(b) as being anticipated by Hilton et al. (U.S. Patent 6,323,317) as set forth at page 10 of the previous Office Action (06 January 2010) is *withdrawn* in view of the amended claim. Claim 4 no longer recites the nucleic acid encoding the SOCS3 amino acid sequence of SEQ ID NO: 4.

5. The rejection of claims 12 and 23 under 35 U.S.C. § 103(a) as being unpatentable over Hilton et al. in view of Lin et al. as set forth at pages 10-13 of the previous Office Action (06 January 2010) is *withdrawn* in view of the amended claims (03 June 2010).

6. The rejections of claim 20 under 35 U.S.C. § 112, first paragraph (enablement) and 35 U.S.C. § 103(a) as being unpatenable over Shouda et al. in view of Hilton et al. and Lin et al. as set forth at pages 5-10 and 13-16 of the previous Office Action (06 January 2010) are *withdrawn* in view of the cancellation of claim 20 (03 June 2010).

New Objections/Rejections

Claim Objections

7. Claim 7 is objected to because of the following informalities:

7a. In claim 7, line 1, the phrase "[a] cell comprising a vector, the vector comprising…" should recite, for example, "[a] cell comprising a vector, wherein the vector comprises...".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8a. Claim 5 is rejected as being indefinite because the claim refers to a single SOCS nucleotide sequence set forth in SEQ ID NO: 11. However, claim 5 depends from claims 3 and

4, which both refer to two different SOCS nucleic acid sequences (i.e., SOCS1 and SOCS3). Hence, it is not clear which specific SOCS (i.e., SOCS1 and SOCS3) the nucleic acid sequence of SEQ ID NO: 11 is referring to.

Maintained Rejections

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 7, 12-14, 16-19, 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or cultured host cell comprising a vector wherein the vector comprises an isolated human nucleic acid encoding a SOCS1 or SOCS3 sequence and a membrane translocating sequence set forth in SEQ ID NO: 2, ***does not reasonably provide enablement for*** a cell comprising the vector. Furthermore, the specification, while being enabling for a method of treating an inflammatory disease in a subject comprising administering a polypeptide comprising a SOCS1 or SOCS3 sequence and a membrane translocation sequence to the subject ***does not reasonably provide enablement for*** a method of preventing an inflammatory disease in a subject comprising administering a polypeptide comprising a SOCS sequence and a membrane translocation sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 7 is directed to a cell comprising a vector comprising the nucleic acid. Claim 12 recites a method of preventing an inflammatory disease in a subject comprising administering the polypeptide of claim 1 to a subject. Claim 13 recites that the subject is a subject with an inflammatory disease or at risk for presenting with an inflammatory disease. Claim 16 recites that the inflammation is associated with an infection. Claim 21 recites that the polypeptide is administered prior to or after surgery. Claim 22 recites that the polypeptide is administered to the subject prior to or after contact with an infectious biological weapon. Claim 23 recites a method of preventing an inflammatory disease in a patient comprising administering an isolated polypeptide comprising a cell penetrating suppressor of cytokine signaling 1 or 3 (CP-SOCS1 or CP-SOCS3) polypeptide to a patient.

Applicant's arguments (03 June 2010), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Regarding the Examiner's interpretation of the claims as reading upon host cells in the context of multicellular, transgenic organisms and host cells intended for gene therapy, Applicant argues that claim 7 has been amended to recite the term "comprising". At the top of page 11, Applicant also indicates that claim 7 has been amended to include the recitation of the sequences corresponding to the SOCS and membrane translocating sequences which are encoded by the vector of claim 6.

Applicant's argument has been fully considered but is not found to be persuasive. Although claim 7 has been amended to recite "[a] cell comprising a vector", the claim is still interpreted by the Examiner as reading upon isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. At the

top of page 9 of the previous Office Action, the Examiner indicated that this issue could be overcome by amending the claim to recite, for example, "an isolated host cell".

(ii) At page 12 of the Response, Applicant asserts that the construction of a vector expressing a SOCS polypeptide and a membrane translocating sequence and then production, purification, and intracellular delivery of SOCS1 and SOCS3 recombinant proteins in a cell-penetrating form. Applicant refers to pages 51-52 of the specification. Applicant states that the polypeptides expressed from these vectors in producer cells and stringently purified are delivered intracellularly; that these molecules are functional ex vivo in primary bone marrow-derived macrophages or transformed cell lines and in vivo as measured by increased survival of the subject due to attenuation of massive liver inflammation and apoptosis. Applicant contends that in contrast to the Examiner's assertions that the claims are directed to gene therapy, Applicant instead teaches that the replacement of depleted stores of intracellular physiologic anti-inflammatory protein, such as SOCS3, with recombinant, cell-penetrating forms of SOCS which was found to be a feasible alternative to gene transfer of SOCS3. Applicant argues that the essence of intracellular protein therapy approach was based on the data in the specification whereby intracellular delivery of the SOCS molecules are recombinant proteins in cell-penetrating form. Applicant states that the intracellular delivery of the recombinant proteins in cell-penetrating form is taught in the specification and cites MPEP § 2164.02 (citing Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987).

Applicant's arguments have been fully considered but are not found to be persuasive. As indicated in part (i) above, claim 7 is still interpreted by the Examiner as reading upon host cells

in the context of a multicellular, transgenic organism and host cells intended for gene therapy. Although Applicant argues that the replacement of depleted stores of intracellular physiologic anti-inflammatory protein, such as SOCS3, with recombinant, cell-penetrating forms of SOCS which was found to be a feasible alternative to gene transfer of SOCS3, the specification of the instant application clearly teaches that the compositions can be administered in a pharmaceutically carrier and can be delivered to the subject's cells in vivo and/or ex vivo by a variety of mechanisms known in the art (page 22, [76]). The specification continues to state that "[t]he compositions can be introduced into the cells via any gene transfer mechanism, such as, for example, calcium phosphate mediated gene delivery, electroporation, microinjection or proteoliposomes (page 22, [76]). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated nucleic acid encoding a polypeptide comprising a SOCS sequence and a membrane translocation sequence is demonstrated to express the polypeptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the DNA "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Furthermore, the specification does not teach any methods or working examples that indicate a nucleic acid encoding a SOCS sequence and a membrane translocation sequence is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further

experimentation. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a nucleic acid into the cell of an organism. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a nucleic acid in the cell of an organism or be able to produce the protein of interest in that cell.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the polypeptide comprising a SOCS sequence and a membrane translocation sequence and to

introduce and express the nucleic acid in a cell of an organism for therapy; the lack of direction/guidance presented in the specification regarding how to introduce the nucleic acid in the cell of an organism to be able produce that polypeptide; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells; and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(iii) At the bottom of page 13 of the Response, Applicant contends that the specification provides sequences for SOCS molecules and that working examples are provided as to how to express SOCS sequences in bacterial or mammalian cells to produce recombinant proteins in cell-penetrating form for intracellular delivery ex vivo and in vivo. Applicant states that these can then be tested as to whether they are, for example, anti-inflammatory. At page 11 of the Response, Applicant also asserts that three SOCS sequences (SOCS1, SOCS3, and truncated SOCS3 with extended half-life) can be used and provide one of ordinary skill in the art the pertinent disclosure to make and use any SOCS sequence. At the top of page 12 of the Response, Applicant argues that the specification and claims more than meet any enablement requirements and provide Crocker et al. (Sem Cell Dev Biol 19: 414-422, 2008), which summarizes SOCS biology.

Applicant's arguments have been fully considered but are not found to be persuasive. Such broad brush assertions do not constitute adequate guidance to practice the claimed method,

but rather constitute an invitation to experiment empirically to determine how to practice the suggested method to obtain the therapeutic results required by the claims. The specification of the instant application teaches that any SOCS protein, such as SOCS-1, SOCS-2, SOCS-3, SOCS-4, SOCS-5, SOCS-6, or SOCS-7, can be used as the source of the SOCS sequence (page 10, lines 28-29). However, the specification and the prior art do not teach that any SOCS proteins, other than SOCS1 and SOCS3, play a role in reducing inflammation, as required by the instant claims and undue experimentation would be required of one skilled in the art to determine such. The post-filing date reference of Crocker et al. supplied by Applicant does not lend any additional evidence that other SOCS are involved in inflammation. Additionally, a large quantity of experimentation would be required by the skilled artisan to inhibit a cytokine-induced response in a cell or subject by administering a polypeptide comprising any SOCS sequence and MTS (as required by claims 27 and 28) because Larsen et al. indicate that at the present, there seems to be no clear evidence that the expression of SOCS-4, SOCS-5, SOCS-6, and SOCS-7 mRNAs is induced by cytokines, and very little is known about the function and mechanisms of the actions involved (APMIS 110: 833-844, 2002, cited on the IDS of 28 April 2008;; page 834, column 1). Larsen et al. also teach that studies with SOCS-2 in mice suggest a primary role in regulation of growth by GH and IGF-I (page 841, bottom of column 1). Larsen et al. state that "[e]ven though all the SOCS proteins exhibit a similar structure, with a conserved central SH2 domain and a C-terminal SOCS box, the sequence identity between these members reveals an only distant relationship, reflected by variations in tissue expression, expression kinetics, specificity, and not least the different mechanisms of inhibition" (page 842, column 2). Hence, one skilled in the art would not be able to predict that all SOCS proteins have a conserved

function, or that all SOCS proteins would be able to reduce inflammation in a subject. The specification of the instant application does not teach any methods or working examples that indicate any SOCS, other than SOCS3, reduces inflammation or treats any other diseases or disorders. Due to this lack of guidance, a large quantity of experimentation would be required of the skilled artisan to determine the role of SOCS-2, SOCS-4, , SOCS-5, SOCS-6, and SOCS-7 in inflammation.

(iv) It is noted that claims 12 and 23 have been amended in the Response of 03 June 2010 to recite a method of preventing an inflammatory disease. The specification of the instant application teaches that recombinant CP-SOCS3 suppresses systemic inflammation (pages 49-50, Example 4). The state of the art teaches that expression of SOCS1 or SOCS3 reduce inflammation in several different inflammatory diseases (Alexander et al. Annu Rev Immunol 22: 503-529, 2004; see especially page 519;; cited on the IDS of 28 April 2008; see also Hanada et al. Rev Physiol Biochem Pharmacol 149: 72-86, 2003, especially pages 77-80). However, the specification does not disclose any methods or working examples that "prevent" an inflammatory disease in a subject, as required by claims 12-14, 16-19 and 21-25. The term "preventing" is interpreted by the Examiner as meaning that an activity will not occur, i.e., an inflammatory disease will not occur. The limited guidance in the specification is not adequate and is merely an invitation for the skilled artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily prevent an inflammatory disease in subject by administering an isolated polypeptide comprising a SOCS sequence and a membrane

translocating sequence. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration the polypeptide. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed."

Due to the large quantity of experimentation necessary to determine the optimal quantity, duration, and route of administration of SOCS polypeptide to prevent an inflammatory disease; the lack of direction/guidance presented in the specification regarding such; the absence of working examples; the complex nature of the invention; and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-4, 6-11, 27, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilton et al. (U.S. Patent 6,323,317) in view of Lin et al. (WO 99/49879). The basis of this rejection is set forth for claims 1, 3, 4, 6-12, 23, 27, 28 at pages 10-13 of the previous Office Action (06 January 2010).

Applicant's arguments (03 June 2010), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 15 of the Response, Applicant argues that the combination of SOCS and an MTS would not have been obvious to one of skill in the art. Applicant contends that until the filing of the instant application and the inventors' seminal study in 2005 (Jo et al.) on proving their concept of intracellular protein therapy with cell-penetrating form of SOCS3 protein for ex vivo and in vivo intracellular delivery, it would not have been obvious to one of skill in the art. Applicant asserts that Hilton et al. and Lin et al. did not teach, suggest, or provide the motivation for engineering a protein that was able to cross cell membrane and suppress inflammation. Applicant states that Hilton et al. did not provide any teachings that would lead one of ordinary skill in the art to produce a SOCS protein to cross cell membrane. Applicant argues that Hilton et al. and Lin et al. did not propose to test the hypothesis that replacement of depleted stores of intracellular physiologic protein, such as SOCS3, a feasible alternative to gene transfer of SOCS3. Applicant asserts that, as Examiner aptly stated, gene transfer approach practiced by those skilled in the art did not overcome inherent difficulties in facile and controlled delivery of

SOCS3 gene. In contrast, the inventors proposed the concept of intracellular delivery of cell-penetrating forms of SOCS and SOCS3 as a facile and versatile alternative to gene therapy. A fusion protein, as suggested by the Examiner would have required proof of concept difficult to obtain without meticulous selection of bacterial or mammalian expression system for production of such a fusion protein. Applicant contends that the combination of SOCS3 (or SOCS1) with MTS may have precluded its expression or if expressed might rendered the protein insoluble. Such an outcome would have resulted in a protein that could not and would not be delivered intracellularly.

Applicant's arguments have been fully considered but are not found to be persuasive. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, Hilton et al. teach that SOCS proteins are intracellular regulators of cell signaling, wherein modulation of SOCS activity or expression requires administration of agonists, antagonists, or DNA constructs (column 3, lines 27-30; column 31, lines 65-67 through column 32, lines 1-6), it was well known in the prior art that SOCS proteins are intracellular (see for example, Larsen et al. (APMIS 110: 833-844, 2002;; Figure 4), and Lin et al. teach that problems with DNA constructs (such as gene therapy and recombinant viral vectors) were known in the art at the time

the invention was made and could be overcome by fusing an artificial membrane translocating sequence to a target protein for import into the cell (page 3, lines 4-11; page 7, lines 23-29).

Regarding Applicant's argument that a fusion protein would have required proof of concept difficult to obtain without meticulous selection of bacterial or mammalian expression system for production of such a fusion protein, it is noted that the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success (see MPEP 2143.02 and *In re Merck & Co., Inc.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this instant application, the person of ordinary skill in the art reasonably would have expected success because Lin et al. demonstrate the successful import of target proteins into a cell using a membrane translocation sequence (page 38, last example; also, pages 35-37). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

11. Claims 12, 13, 14, 23, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shouda et al. (J Clin Invest 108(12): 1781-1788, 2001) in view of Hilton et al. (U.S. Patent 6,323,317) and Lin et al. (WO 99/49879). The basis for this rejection is set forth for claims 12, 13, 14, 20, 23, 24, and 25 at pages 13-16 of the previous Office Action (06 January 2010).

Applicant's arguments (03 June 2010), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 16 of the Response, Applicant submits that it would not be obvious to one of ordinary skill in the art to combine SOCS and MTS including the Shouda et al. study. Applicant argues that neither Hilton et al. in view of Lin et al. provide the necessary motivation to combine

the SOCS and MTS as taught by Applicant. Applicant asserts that Shouda et al. do not even contemplate therapy by means of intracellular delivery of the SOCS3 protein into a cell for the treatment of rheumatoid arthritis. Applicant indicates that Shouda et al. only contemplate treating the localized symptoms of rheumatoid arthritis by attempting to locally inject their vector. Applicant states that this is in contrast to the instant invention which is directed to the importation of the therapeutic SOCS proteins into cells and can be systemically disseminated throughout various cells, tissues, organs, and fluids rendering a superior therapy. Applicant invites the Examiner to consult a series or reports which support the originality of the invention and document that the invention requires specifically defined condition for production, purification, and administration of cell-penetrating forms of SOCS1, SOCS3, and its long-acting truncation mutant (Jo et al. 2005 Nat Med; DeGiandomenico 2009 Science Signaling; Fletcher et al. 2010 J Biol Chem).

Applicant's arguments have been fully considered but are not found to be persuasive. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, Shouda et al. teach that SOCS3 adenovirus reduces the severity of arthritis and joint swelling and conclude that adenovirus-mediated gene transfer of the SOCS3 gene is a promising means of

treatment (abstract; Figures 5, 6; page 1787, column 1, second full paragraph; page 1788, top of column 1); and Lin et al. teach that problems with DNA constructs (such as gene therapy and recombinant viral vectors) were known in the art at the time the invention was made and could be overcome by fusing an artificial membrane translocating sequence to a target protein for import into the cell (page 3, lines 4-11; page 7, lines 23-29).

In response to applicant's arguments against the references individually (particularly, Shouda et al.), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It would have been obvious to the skilled artisan at the time the invention was made to modify the method of treating rheumatoid arthritis of Shouda et al. by substituting the recombinant adenovirus carrying SOCS3 cDNA for a fusion polypeptide comprising SOCS3 and a membrane translocation sequence as taught by Hilton et al. and Lin et al. The person of ordinary skill in the art reasonably would have expected success because Lin et al. demonstrate the successful import of target proteins into a cell using a membrane translocation sequence (page 38, last example; also pages 35-37). While Applicant's peer-reviewed paper, Jo et al. 2005, is interesting and reports many of the findings of the instant application, the claimed invention as a whole is still clearly *prima facie* obvious over the prior art. It is noted that DeGiandomenico 2009 and Fletcher et al. 2010 are incomplete citations and have not been submitted with the Response of 03 June 2010 for review by the Examiner.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
04 August 2010

/Bridget E Bunner/
Primary Examiner, Art Unit 1647